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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,919	06/14/2002	Michael Panaccio	DAVI151.001APC	1078

7590 09/10/2004

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,919	PANACCIO ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *5,9,12,15,16 and 27-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10,11,13,14 and 17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/9/02, 8/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response

1. Applicant's response to restriction filed on 6/18/2004 is acknowledged. Claims 1-48 are pending in the application.

Election/Restriction

2. Applicant's election of Group I, Claims 1-4, 6-8, 10, 11, 13, 14, and 17-26 with traverse with respect to SEQ.ID.NO: 1 is acknowledged. The traversal is on the ground(s) that all of the groups of claims relate to therapeutic compositions for the treatment of disease caused by *L. intracellularis.* Further, the invention provides a novel polypeptide from *L. intracellularis* which encodes hemolysin peptide, polypeptide or protein. The hemolysin polypeptide is useful as an antigen and the present invention provides various methods associated with the polypeptide. Applicant requests the examiner to prosecute all the groups, as it is well-accepted practice in the Office to prosecute all the groups in a single application because search and examination would not be an undue burden. This is not found persuasive.

The examiner has restricted the claims based on the restriction rules under 35U.S.C. 121 and 372. As indicated in the previous office action, Panaccio W0 97/20050 discloses an isolated polypeptide comprising a Lawsonia variant or recombinant polypeptide comprising a Lawsonia variant (see example 14 and claims of W0 97/20050) and thus read on a variant of claimed invention. Various different molecular weight proteins recognized by western blots (see example 14) in the prior art read on variants that mimics T-cell or B-cell epitopes of *Lawsonia* because the proteins are from *Lawsonia intracellularis* and reacted with antibodies indicating the presence of B-cell epitopes. These proteins were reacted to antibodies obtained from vaccinated sera (see example 14) indicating that these are immunogenic polypeptides having T-cell or B-cell epitopes of *Lawsonia* as they reacted with serum obtained from vaccinated

samples. Therefore, no special technical feature exists for Group I as defined by PCT Rule 13.2, because it does not define a contribution over the prior art. Therefore, it does not constitute a special technical feature by definition and hence unity of invention is lacking. Therefore, the technical feature of linking groups I-VII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art and hence unity of invention is lacking. Therefore, polypeptide and various methods using polypeptide are considered different invention.

Concerning the burden of search is merely one indication of the burdensome nature of the search involved. The protein database searches required by each of the sequences and the literature searches for each of the sequences, both of which are particularly relevant in this art, are not co-extensive and are much more important in evaluating the burden of search. For example, search and examination issues for different proteins and vaccines are different. Clearly different searches and issues are involved in the examination of each group.

Status of claims

3. Claims 1-48 are pending.

Claims 1-4, 6-8, 10, 11, 13, 14, and 17-26 are under examination to the extent they read on the elected invention of SEQ.ID.NO: 1.

Claims 5, 9, 12, 15, 16 and 27-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Priority

4. This application is a 371 of PCT/AU00/00439 filed on 5/11/2000. Applicant claims domestic priority to provisional application 60/134,022 filed on 5/13/1999 is acknowledged.

Information Disclosure Statement

5. Information Disclosure Statements filed on 4/9/02 and 8/16/02 are acknowledged and a signed copy of each is attached to this Office action.

Copies of the following references cited in the August 16, 2002 IDS were not submitted with the IDS:

Ausubel et al., Ed current Protocols in Molecular Biology" Alan R Bliss Inc.

Cole et al., Monoclonal Antibodies in cancer therapy.

Dayhof, M.D. Nat. Biomed. Res. Found.

Gabriel et al., Vaccince, 95 (1995).

Mcpherson et al., A Practical Approach.

Sambrook et al., Molecular Cloning: A laboratory manual in the IDS or August 12, 2002.

Thus, the Applicant has not met the requirements under 37 CFR 1.98 for these references. They have therefore been crossed out from the IDS and have not been considered.

Claim Rejection - 35 U.S. C. 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 6-8, 10, 11,17- 22 and 25-26 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the revised guidelines on written description available at www.uspto.gov (O.G. published January 30, 2001). This is a written description rejection.

The claims 1-4, 6-8, 10, 11 and 17-20 are drawn to an isolated or recombinant immunogenic polypeptide comprising a Lawsonia spp. hemolysin polypeptide, a variant, or a truncated variant thereof, wherein said variant or truncated variant mimics or cross-reacts with a B-cell or T-cell epitope of Lawsonia spp. hemolysin polypeptide, wherein the Lawsonia spp. is *L. intracellularis.* Claims are also drawn to an isolated or recombinant immunogenic polypeptide comprising: (i) a peptide, oligopeptide or polypeptide comprising an amino acid sequence Which has at least about 70% sequence identity to the amino acid sequence set forth in SEQ ID NO: 1, (ii) a peptide, oligopeptide or polypeptide which complises an amino acid sequence having at least about 50% sequence identity to amino acid residues 1 to 50 of SEQ ID NO: 1; or (iii) a homologue or derivative of (i) or (ii) which mimics a B-cell or T-cell epitope of a Lawsonia spp. hemolysin polypeptide, wherein said polypeptide elicits the production of antibodies against Lawsonia spp.

Claims 21, 22 and 25- 26 are drawn to a vaccine composition for the prophylaxis or treatment of infection of an animal by Lawsonia spp., said vaccine composition comprising an effective amount of an immunogenic component comprising an isolated or recombinant polypeptide having at least about 70% sequence identity to the amino acid sequence set forth in SEQ ID NO: 1 or at least about 50% sequence identity to amino acid residues 1 to 50 of SEQ ID NO: 1 or an immunogenic homologue, or derivative thereof which is immunologically cross-reactive with *Lawsonia intracellularis* and one or more carriers, diluents or adjuvants suitable for veterinary or pharmaceutical use, wherein the vaccine composition comprises an isolated or recombinant polypeptide comprises the amino acid sequence set forth in SEQ ID NO:1 or the amino acid sequence encoded by the hemolysin-encoding nucleotide sequence of PALKI2 (ATCC 207195), wherein the immunogenic composition comprises an amino acid residues about 1 to about 50 of SEQ ID NO:1.

The specification describes as part of the invention, an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The specification teaches that the full-length protein comprises 251 amino acids as set forth in SEQ.ID.NO: 1 and is useful in diagnosing infection caused by *Lawsonia intracellularis* in pigs. However, the immunological function of this

polypeptide in assessing Lawsonia infection has not yet been identified. Further, the specification does not disclose

1) an isolated or recombinant immunogenic polypeptide comprising a *Lawsonia spp* hemolysin polypeptide, a variant, or a truncated variant thereof, wherein said variant or truncated variant mimics or cross reacts with a B-cell or T-cell epitope of Lawsonia spp hemolysin polypeptide or

2) a vaccine composition comprising a *Lawsonia spp* hemolysin polypeptide, a variant, or a truncated variant thereof, wherein said variant or truncated variant mimics or cross reacts with a B-cell or T-cell epitope of Lawsonia spp hemolysin polypeptide or

3) an isolated or recombinant immunogenic polypeptide or a vaccine composition comprising

i. a peptide, oligopeptide or polypeptide comprising 70% sequence identity to SEQ.ID.NO: 1

ii) a peptide, oligopeptide or polypeptide comprising 50% sequence identity to amino acid residues 1 to 50 of SEQ.ID.NO: 1;

iii) a homologue or derivative of (a) or (b) which mimics or cross reacts with a B-cell or T- cell epitope of Lawsonia spp hemolysin polypeptide

iv) an isolated polypeptide comprising 1 to 50 amino acids of SEQ.ID.NO: 1 (the examiner considers all these variants and hereafter will be referred to variants). Therefore, said variants do not meet the guidelines on written description.

The specification fails to disclose any substitution, insertion or deletion or change in (i) a polypeptide SEQ.ID.NO: 1 to obtain a variant having 70% or 50% identity to SEQ.ID.NO: 1 or variants or homologues of SEQ.ID.NO: 1. The specification does not describe any use of said variants as claimed (comprising, open language) in identifying *L.intracellularis* infection. None of the above variants meet the written description provision of 35 U.S.C. 112, first paragraph. *Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111*, makes clear that "applicant must convey with

reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, the specification fails to teach the claimed variants and does not satisfy the written description guidelines because an isolated polypeptide comprising (open language) said variants plus unlimited and unknown amino acids of SEQ.ID.NO: 1 and an isolated polypeptide comprising an amino acid sequence having 70% or 50% % sequence identity to SEQ.ID.NO: 1 plus unlimited and unknown amino acids would result in unknown variants without sufficient structure and completely lacking identifying characteristics such as function. Thus, variants as claimed are broader than SEQ.ID.NO: 1 and do not appear to have sufficient structural characterization and lack any identifying characteristics (function). Further, inducing an immune response is not an identifying characteristic (function) of a fragment because there are many fragments with the same function in a polypeptide and such variants are not distinguishable from each other. Thus variants as claimed are uncharacterized by this specification and are not asserted to belong to any known family of proteins such as outer membrane proteins of *L.intracellularis.* The specification fails to teach the structure or relevant identifying characteristics sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See *Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016.* One cannot describe what one has not conceived.

See *Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.
The actual biological function of isolated hemolysin polypeptide SEQ ID NO: 1 is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. *USPQ2d 1111* makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

The specification only discloses hemolysin polypeptide comprising the amino acid sequence SEQ ID NO: 1 which corresponds to the polynucleic acid sequence SEQ ID N0: 2. Thus, hemolysin polypeptide comprising the amino acid sequence SEQ ID NO: 1 meet the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below. The specification fails to teach the claimed variants and they do not exist as an invention independent of their function in encoding a protein. The actual structure or other relevant identifying characteristics of each variant including homolog, analogue or derivative having the claimed properties can only be determined empirically by actually making every recited variability (i.e. variants,) and testing each to determine whether such a variant has any particularly disclosed properties of a protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function. This specification does not teach such variants, and the art is devoid of such said variants of SEQ ID

NO: 1, with undetermined function. There is no written description support for variants as claimed.

8. Claims1-4, 6-8, 10, 11, 17- 26 are rejected under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide or a recombinant immunogenic polypeptide comprising the amino acid sequence SEQ ID NO: 1 of *L.intracellularis* hemolysin polypeptide or an immunogenic composition comprising the amino acids sequence SEQ ID NO: 1 of *L.intracellularis* hemolysin polypeptide and one or more carriers, diluents or adjuvants suitable for veterinary or pharmaceutical use does not reasonably provide enablement for an

1) an isolated or recombinant immunogenic polypeptide comprising a *Lawsonia spp* hemolysin polypeptide, a variant, or a truncated variant thereof, wherein said variant or truncated variant mimics or cross reacts with a B-cell or T-cell epitope of Lawsonia spp hemolysin polypeptide or

2) a vaccine composition comprising a *Lawsonia spp* hemolysin polypeptide, a variant, or a truncated variant thereof, wherein said variant or truncated variant mimics or cross reacts with a B-cell or T-cell epitope of Lawsonia spp hemolysin polypeptide or

3) an isolated or recombinant immunogenic polypeptide or a vaccine composition comprising

i. a peptide, oligopeptide or polypeptide comprising 70% sequence identity to SEQ.ID.NO: 1

ii) a peptide, oligopeptide or polypeptide comprising 50% sequence identity to amino acid residues 1 to 50 of SEQ.ID.NO: 1;

iii) a homologue or derivative of (a) or (b) which mimics or cross reacts with a B-cell or T- cell epitope of Lawsonia spp hemolysin polypeptide

iv) an isolated polypeptide comprising 1 to 50 amino acids of SEQ.ID.NO: 1 (the examiner considers all these variants and hereafter will be referred to variants). The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims have been discussed supra as above in Paragraph # 7.

The specification fails to provide an enabling disclosure o for the full scope of claimed polypeptide variants other than peptide SEQ.ID.NO: 1 itself because it fails to provide any guidance regarding how to make and use the variants (any amino acid sequence selected from an amino acid sequence which has 70% or 50% sequence identity to SEQ.ID.NO: 1 etc).

The instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention is preparing recombinant polypeptide from *L. intracellularis* only. The invention is drawn to an isolated protein as set forth in SEQ ID NO: 1 which is encoded by *L. intracellularis* polynucleotide, SEQ.ID.NO: 2 (pALK12, ATCC 207195). The specification also teaches that this full-length protein contains 251 amino acids. The specification discloses the claimed polypeptide could be used to identify *L. intracellularis infection* and as an immunogen and formulating the compositions in Freund's adjuvant to immunize mice for preparing antibodies.

The state of the art in *L. intracellularis is* devoid of making or using fragments of recombinant peptides or variants as claimed. Moreover, protein chemistry is probably one of

the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid sequences (i.e. fragments) for different aspects of biological activity cannot be predicted a priori and must be determined empirically on a case-by-case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produces proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Thus, it is apparent that change in a peptide can lead to loss of binding property of that peptide.

The specification provides no working examples demonstrating (i.e., guidance) enablement for an isolated polypeptide comprising a sequence having 70%, or 50% sequence

identity to SEQ.ID.NO: 1 or an immunogenic fragment of a polypeptide comprising at least 1-50 amino acids of SEQ.ID.NO: 1, immunogenic composition comprising said variants of SEQ ID NO: 1. Furthermore, it is unclear whether isolated polypeptide comprising a sequence having 70%, or 50% sequence identity to SEQ.ID.NO: 1 or an immunogenic fragment of a polypeptide comprising at least 1-50 amino acids of SEQ.ID.NO: 1 of can be used for identifying *L. intracellularis* infection. Thus, peptides comprising *L. intracellularis* must be considered highly unpredictable, requiring a specific demonstration of efficacy on a case-by-case basis.

With respect to vaccine composition as recited in claims 21-26, the specification provides no information on the protective immunogenicity of the claimed polypeptide, fragments, the variants or the ability to protect the animal from disease. The specification fails to teach that the claimed polypeptide or fragments or variants are capable of generating a humoral or cellular immune response. The specification also fails to teach that the immune/antibody response to the polypeptide produced by the claimed polypeptide alone or in combination with adjuvants or carriers provides protection against infection in any acceptable animal model. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient to provide for enablement of vaccines. This specification fails to teach protective immune response generated by said isolated polypeptide --vaccine. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, 5.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed polynucleotide

encoding polypeptides or fragments thereof alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. The specification fails to teach that the claimed polynucleotide encoding a polypeptide peptide or fragment or variant thereof are able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize other similar nucleic acids as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. (*Genentech Inc. v. Novo Nordisk A/5 Ltd., 42 USPQ2d 1001*). Moreover, the specification must have been enabling at the time the invention was made-and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright, 27 U5PQ2d 1510*).

The state of the art indicates that very little is known about the humoral and, especially, cell-mediated immune response in pigs exposed to Lawsonia intracellularis. Pathogenesis of L. intracellularis has not been well investigated; however, organisms cultured in vitro have been used successfully to reproduce the disease in vivo. This bacterium has a tropism for intestinal epithelial cells, and the major pathological consequence of infection is hyperplasia of infected epithelial cells. The specific bacterial determinants, which confer pathogenicity and cause these distinctive pathological effects, are not known (see McCluskey et al, Infect Immun 2002 Jun; 70(6): 2899-907). Bacterial attachment and entry occur via the apical surface of immature epithelial cells in a process which appears to require a specific bacterial ligand-receptor interaction and once inside the cell, the bacteria escape from the vacuolar compartment into the cytoplasm, where they multiply and spread from cell to cell following cell division. At present, the determinants used by *L. intracellularis* to enter the cell, escape the vacuole, multiply intracytoplasmically, and modulate host cell function are not known. Therefore, the claimed

outer-membrane protein induces an effective immune response such that it can be used, as a vaccine composition is not predictable in this underdeveloped art. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for any *in vivo* uses of the claimed protein.

In the absence of teachings that the claimed polypeptide can generate a protective immune response, which is effective in preventing the infection or disease, the specification is not enabled for vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

9. Claims 13,14 and 23, 24 are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention. This is a rejection for Deposit without a promise for availability. The nucleic acid encoding the hemolysin in the pALKI2 plasmid is required to practice the claimed invention. This is because, the Applicant has claimed inventions comprising the polypeptide encoded by the sequence of the plasmid, and has not provided the sequence in the application. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the claimed/described plasmid, See 37 CFR 1 .802.

The specification does not provide a repeatable method for obtaining the plasmid and it is not apparent if it is readily available to the public. Applicant's deposit statement on specification page 57 does not indicate the extent of public availability. If the deposit is made under the term

of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

of the Budapest Treaty, then an affidavit or declaration by applicants or someone asociated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4, 6-8, 10, 11,17-22 and 25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by McOrist et al, Infect Immun. 1989 March; 57 (3): 957–962.

The claims 1-4, 6-8, 10, 11 and 17-20 are drawn to an isolated or recombinant immunogenic polypeptide comprising a Lawsonia spp. hemolysin polypeptide, a variant, or a truncated variant thereof, wherein said variant or truncated variant mimics or cross-reacts with a B-cell or T-cell epitope of Lawsonia spp. hemolysin polypeptide, wherein the Lawsonia spp. is *L. intracellularis.* Claims are also drawn to an isolated or recombinant immunogenic polypeptide comprising: (i) a peptide, oligopeptide or polypeptide comprising an amino acid sequence Which has at least about 70% sequence identity to the amino acid sequence set forth in SEQ ID NO: 1, (ii) a peptide, oligopeptide or polypeptide which complises an amino acid sequence having at least about 50% sequence identity to amino acid residues 1 to 50 of SEQ ID NO: 1; or (iii) a homologue or derivative of (i) or (ii) which mimics a B-cell or T-cell epitope of a Lawsonia spp. hemolysin polypeptide, wherein said polypeptide elicits the production of antibodies against Lawsonia spp. in a porcine or avian animal, wherein said polypeptide confers a protective immune response against Lawsonia spp. in a porcine or avian animal, wherein said protective immune response is induced in a porcine animal, wherein the Lawsonia spp. is *L. intracellularis.*

Claims 21, 22 and 25-26 are drawn to a vaccine composition for the prophylaxis or treatment of infection of an animal by Lawsonia spp., said vaccine composition comprising an effective amount of an immunogenic component comprising an isolated or recombinant polypeptide having at least about 70% sequence identity to the amino acid sequence set forth in SEQ ID NO: 1 or at least about 50% sequence identity to amino acid residues 1 to 50 of SEQ ID NO: 1 or an immunogenic homologue, or derivative thereof which is immunologically cross-reactive with *Lawsonia intracellularis* and one or more carriers, diluents or adjuvants suitable for veterinary or pharmaceutical use, wherein the immunogenic component comprises an amino acid residues about 1 to about 50 of SEQ ID NO:1.

The transitional limitation "comprises" similar to the limitations, such as, "has","includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Molecular Research Corp. v. CBS, Inc., 793 F2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App.1948)* ("comprising" leaves "the claim open. for the inclusion of unspecified ingredients even in major amounts".

McOrist et al disclose an isolated polypeptide profiles obtained with each Campylobacter species such as *C. mucosalis, C. hyointestinalis, C. jejuni*, C. *coli* and Campylobacter-like organism (also known as Lawsonia intracellularis in later publications by McOrist1995). The prior art further identifies that the protein profile obtained from Campylobacter-like organism (see figure 1) was distinct and different from other species of Campylobacter such as *C. mucosalis, C. hyointestinalis, C. jejuni*, C. *coli.* This indicates that the intracellular Campylobacter-like organism (later known as *L.intracellularis*) associated with proliferative enteropathy may be a novel bacterium with significant antigenic differences from the other Campylobacter species previously associated with the disease. Isoelectric focusing results suggested that Campylobacter like organisms in proliferate enteritis lesions possess a specific component of pI 4.5 (see in figure 4) with an antigenic site to that of the 25KD to 27KD (see figure 1 below) component detected in preparations in reducing gels. Therefore, it is likely that the components detected by the two methods represent the same structural component. Isoelectric focusing is a nondenaturing method, indicating that there is one major antigen and that the sodium dodecyl sulfate-polyacrylamide gel electrophoretic procedure denatures the antigen to 25-27kD. The absence of 25 to 27kD (PI 4.5) components in other *C. mucosalis, C. hyointestinalis, C. jejuni*, C. *coli* suggests that these organisms are antigenically different from known *C. mucosalis, C. hyointestinalis, C. jejuni*, C. *coli* and (see figure 4) and later studies recognized this Campylobacter-like organism as L.intracellularis.

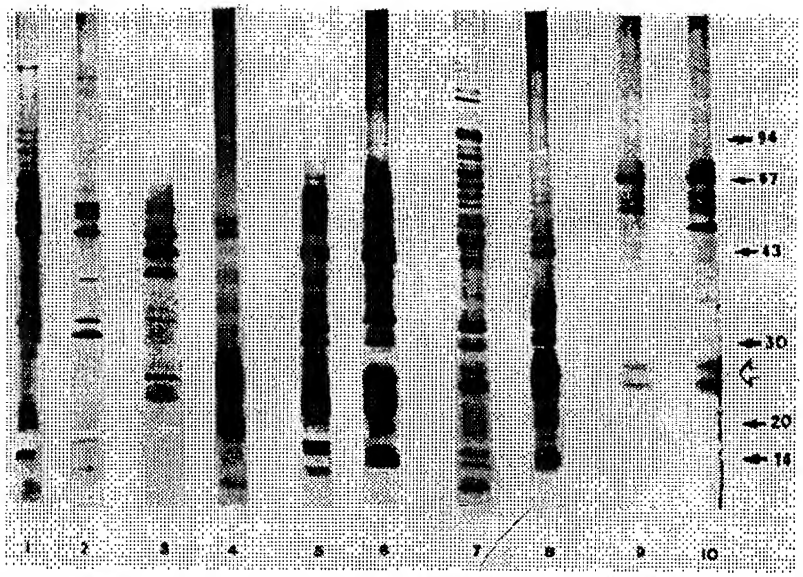

FIG. 1. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis preparations of *Campylobacter* spp. and purified *Campylobacter*-like organisms. Lanes: 1, outer membrane preparation of *C. mucosalis* 1248/72; 2, outer membrane preparation of *C. mucosalis* 124/73B4; 3, outer membrane preparation of *C. hyointestinalis* 124/73A4; 4, sonicated preparation of *C. hyointestinalis* 9AL3; 5, outer membrane preparation of *C. jejuni* 1268/84J; 6, sonicated preparation of *C. jejuni* 664/83; 7, sonicated preparation of *C. coli* 9BF2; 8, sonicated preparation of *C. coli* 9AF3a; 9, whole-cell preparation of *Campylobacter*-like organisms purified from mucosa 284/86 by homogenization, filtration, and passage through a wheat germ agglutinin-agarose column; 10, sonicated preparation of *Campylobacter*-like organisms purified from mucosa 284/86 as described for lane 9. Silver stain; molecular weights are expressed in thousands. The open arrow indicates the 25K and 27K bands.

The lower-molecular-weight OMP 25 kD to 27kD appears to be same as the claimed polypeptide of claim 1 specifically an isolated polypeptide comprising a Lawsonia spp variant, Therefore, 25 kD to 27kD protein is same as hemolysin polypeptide and thus read on the claimed invention. The isolated antigen migrating between 25kD- 27 kD on SDS-PAGE meet the limitations of the claims 1-4, 6-8, 10, 11,13,14 and 17-20 (figure 1) because the disclosed 27kD antigen is from Lawsonia species and thus meet the limitations of hemolysin polypeptide or a variant (the broadly claimed polypeptide having 251 amino acids is almost equivalent to 27kD of the prior art polypeptide since each amino acid molecular weight is 110 daltons). Since the polypeptide is isolated from pigs that have necrotic lesions with proliferative enteropathy, the sale polypeptide read on "hemolysin" polypeptide and it also reads on immunogenic polypeptide as the polypeptide binds to antisera raised against sonicated Campylobacter-like organism (Lawsonia spp) as shown in figure 2 below.

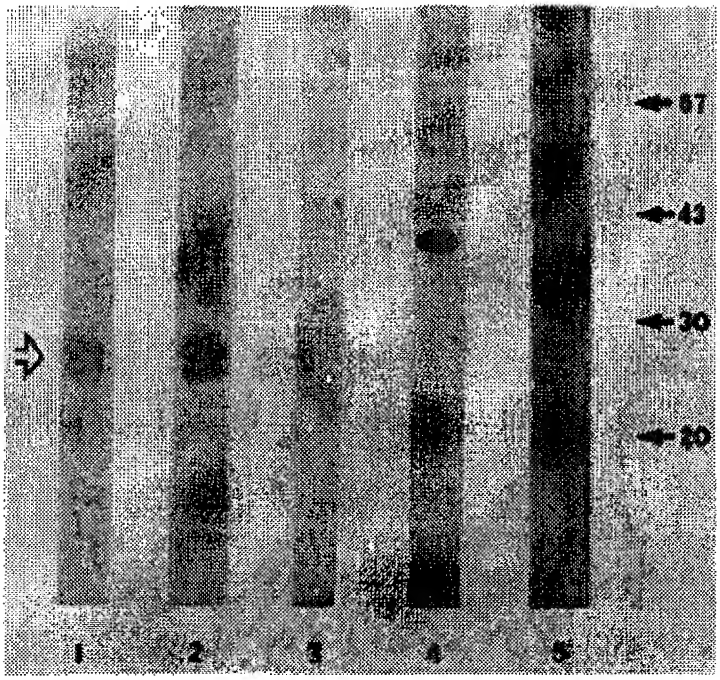

FIG. 2. Immunoblot analysis of rabbit antiserum to *Campylobacter*-like organisms from mucosa 1269/76 reacted against *Campylobacter*-like organisms and *Campylobacter* spp. Lanes: 1, sonicated preparation of *Campylobacter*-like organisms purified from mucosa 284/86 by homogenization, filtration, and passage through a wheat germ agglutinin-agarose column; 2, sonicated preparation of *Campylobacter*-like organisms partly purified from mucosa 284/86 by homogenization and filtration; 3, sonicated preparation of *C. mucosalis* 1248/72; 4, outer membrane preparation of *C. jejuni* 1268/84J; 5, sonicated preparation of *C. coli* 9BF2. Molecular weights are expressed in thousands. The open arrow indicates the 25K and 27K bands.

In the absence of evidence to the contrary that the disclosed polypeptide mimics or cross-reacts with a B-cell or T-cell epitope of Lawsonia spp. hemolysin polypeptide as this 27kD protein reacted with rabbit antisera (see figure 4 below) or monoclonal antibodies prepared against the intracellular Campylobacter-like organisms (i.e., immunogenic, induces immune response) showed strong reactions. Antisera to other Campylobacter species isolates did not react with

preparations of intracellular organisms.

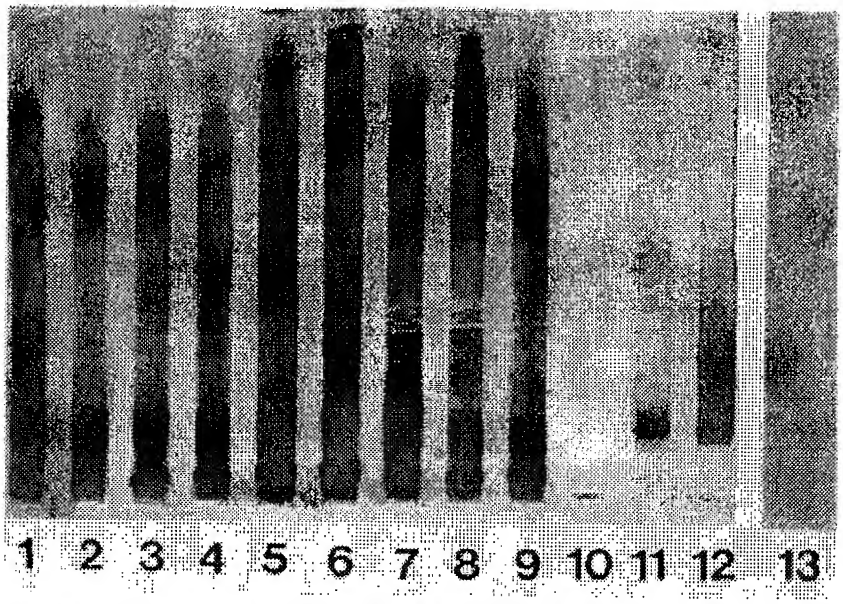

FIG. 4. Isoelectric-focusing gel analysis (lanes 1 to 12; silver stain) and immunoblot analysis (lane 13) of preparations of *Campylobacter*-like organisms. Lanes: 1, sonicated preparation of *C. mucosalis* 1248/72; 2, sonicated preparation of *C. mucosalis* 124/73B4; 3, sonicated preparation of *C. hyointestinalis* 124/73A4; 4, sonicated preparation of *C. hyointestinalis* 9AL3; 5, sonicated preparation of *C. jejuni* 1268/84J; 6, sonicated preparation of *C. jejuni* 664/83; 7, sonicated preparation of *C. coli* 9AF3a; 9, sonicated preparation of *C. coli* NCTC 11353; 10, isoelectric marker, pI 4.0; 11, sonicated preparation of *Campylobacter*-like organisms from mucosa 284/86; 12, sonicated preparation of *Campylobacter*-like organisms from mucosa 761/86; 13, monoclonal antibodies in supernatant fluid IG4, reacted against *Campylobacter*-like organisms from mucosa 284/86.

When producing an isolated 25-27kD polypeptide as discussed above, the composition would inherently have a carrier present, i.e., buffer for pharmaceutical use as required by claim 21. Therefore, the composition comprising an isolated 25-27kD polypeptide in buffer read on vaccine composition of claims 21, 22, and 25-26.

In the absence of evidence to the contrary the disclosed prior art composition and the claimed composition are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed composition with the composition of the prior art, the burden

is on applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art. It is acknowledged that weight is given to every term in claims. This is why the instant claims drawn to vaccine composition are scrutinized differently from a composition claim under 112, first paragraph. However, under prior art rejections, the term vaccine compositions must be weighed with the structural limitations of the claim. If the vaccine composition merely comprises a known composition, the term carries little weight absent evidence of structural difference. Of course, the existence of an unobvious structural difference would define over the prior art. Here, the prior art teaches the same composition as claimed. *In re Thorpe, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). In re Marosi, 218 U.S.P.Q. 289, 293-293 (C.A.F.C. 1983). In re Best, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). In re Brown, 173 U.S.P.Q. 685, 688 (C.C.P.A. 1972).*

Remarks

12. No claims are allowed.

SEQ.ID.NO: 1 appears to be free of prior art.

Conclusion

13. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A

message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Padma Baskar 9/7/04.

Padma Baskar Ph.D.